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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,791	11/10/2003	Kenneth Chien	ST-UCSD3230-1	5197

7590 05/23/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
05/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,791	CHIEN ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,24-31 and 36-38* is/are pending in the application.

4a) Of the above claim(s) *25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-19, 24, 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 2/28/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 18-19, 24-31, 36-38 are pending. Claims 25-31 are withdrawn. Claims 1-17, 20-23, 32-35 are canceled. Claims 18-19, 24, 36-38 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19, 24, 36-38 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 18 is directed to a method for treating a loss of cardiac muscle contractility associated with heart failure comprising: delivering an expression construct to cardiomyocytes in a mammalian host suffering from heart failure, wherein the expression construct provides an expressible polynucleotide encoding a phospholamban (PLB) molecule having a single point mutation consisting of S16E, wherein expression of a therapeutic level of the polynucleotide stimulates improved cardiac muscle contractility. Claims 19 and 24 limit the expression construct to a viral vector. Claim 36 is directed to a method for treating a loss of cardiac muscle contractility associated with heart failure comprising: delivering, via intracoronary administration, an expression construct to cardiomyocytes in a mammalian host suffering from heart failure, wherein the expression construct provides an expressible polynucleotide encoding a

phospholamban molecule having a point mutation consisting of S 16E, wherein expression of a therapeutic level of the polynucleotide stimulates improved cardiac muscle contractility. Claims 37 and 38 limit the expression construct to a viral vector.

The specification discloses the amino acid sequence of an H6-PLB (S16E mutant)-ANT protein and an H6-PLB (V49A mutant)-ANT protein (SEQ ID: Nos. 18 and 19 respectively) (specification p 31, lines 23-24). However the specification fails to provide guidance for delivering an expression construct to cardiomyocytes by any and all routes of administration in a mammalian host suffering from heart failure, wherein the expression construct provides an expressible polynucleotide encoding S16E, wherein expression of a therapeutic level of the polynucleotide stimulates improved cardiac muscle contractility as claimed in the independent claim 18. In addition, the specification fails to provide guidance for delivering an expression construct to cardiomyocytes via intracoronary route in a mammalian host suffering from heart failure, wherein the expression construct provides an expressible polynucleotide encoding S16E, wherein expression of a therapeutic level of the polynucleotide stimulates improved cardiac muscle contractility as claimed in the independent claim 36. The guidance provided by the instant specification fails to correlate the disclosed amino acid sequence of S16E (SEQ ID NO: 18) to the delivery of an expression construct encoding for the S16E mutated PLB (SEQ ID NO: 18) to cardiomyocytes in vivo, expressing a therapeutic level of the protein in vivo resulting in treatment of loss of cardiac muscle contractility associated with heart failure. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed method for treating loss of cardiac muscle contractility associated with heart failure. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

As a first issue the instant invention relates to treatment of loss of cardiac muscle contractility associated with heart failure via a method of gene therapy using a construct encoding a phospholamban (PLB) molecule having a single point mutation consisting of S16E to cardiomyocytes, in vivo. The specification discloses the protein sequence of the H6-PLB (S16E mutant)-ANT protein (SEQ ID. Nos. 18) (specification p 31, lines 23-24). The specification fails to provide guidance with regard to delivering via any route or intracoronary route of administration said construct to cardiomyocytes in vivo, wherein the expression of a therapeutic level of the polynucleotide stimulates improved cardiac contractility resulting in the treatment of a loss of cardiac muscle contractility associated with heart failure.

The art teaches that mutant S16E PLB gene therapy is an unpredictable art with respect to targeting cardiomyocytes in vivo, by any and all routes of administration of the S16E PLB, or by intracoronary route resulting in expression of a therapeutic level of S16E PLB protein in vivo, necessary to provide treatment for loss of cardiac muscle contractility associated with cardiac heart failure. For example, cardiomyocytes, being post-mitotic and terminally differentiated cells, present their own unique challenges and several methods for myocardial gene delivery each presents its own limitations and benefits (**Thompson et al,** Annals of Medicine, 36(Suppl 1): 106-115, 2004) (p 109). For example, direct myocardial injection is burdened with the delivered gene expressing only in and around the small region of myocardium surrounding the needle tack, or pericardial injection is an effective means of transfection in rats and could be proved useful for minimally invasive human delivery if large animal models show similar results (**Thompson et al,** (p 109).

With respect to use of viral vectors for cardiac gene transfer **Thompson** reports several limitations such as short duration of expression, small insert capacity, difficulty in production of high tier stock, low ability to infect non-dividing cells and low efficiency of transfection (p 111,

and Table 1).

Barbato et al, (Critical Reviews in Clinical Laboratory Sciences, 40(5): 499-545, 2003) while reviewing the status of the role of gene therapy in the treatment of cardiovascular diseases notes the challenge of gene therapy is the actual delivery of the genetic material into the targeted tissue in sufficient quantities to result in the synthesis of adequate quantities of gene product to elicit the desired therapeutic action while limiting systemic and/or local toxicity (p 501, under vectors). Vectors differ in transfection efficiency, immunogenicity and ability to transduce dividing or quiescent cells (**Barbato et al,** p 501, 2nd paragraph under vectors). For example, the transient nature of transgene expression with adenoviral vectors may limit the use of these vectors to the treatment of acute vascular injury and have less utility in treating chronic or progressive disorders such as heart failure and atherosclerosis (**Barbato et al,** p 504, 2nd paragraph). **Beck et al,** (Current Gene Therapy,4: 457-467, 2004) reports the technical challenges related to cardiovascular gene transfer are still significant with respect to (i) efficiency of gene delivery, (ii) achievement of high and stable level of transgene expression in a specific cell-type and (iii) design and administration tools and vectors that are safe for clinical application (p 463, bridge 1st to 2nd column). Therefore the prior art challenges the underlying assumption that the S16E mutated PLB transgene will be expressed at sufficient therapeutic levels at the targeted cardiomyocytes, in vivo, for treating loss of cardiac muscle contractility associated with heart failure. Thus, while progress has been made in recent years for gene transfer in vivo, vector targeting to cardiomyocytes in the heart tissue in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art.

As a second issue, the instant invention encompasses the treatment of loss of cardiac muscle contractility associated with heart failure by administering any viral vector encoding the S16E mutant of phospholamban gene. Considering the complexities involved the etiology of

loss of cardiac muscle contractility associated with heart failure instant specification fails to provide an enabling disclosure, which establishes the S16E mutant form of phospholamban gene is capable of treating loss of cardiac muscle contractility associated with heart failure. While progress has been made in recent years for in vivo gene transfer, vector targeting in vivo to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that could not have been overcome by routine experimentation. These include, the fate of DNA itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (**Ecke et al Goodman & Gilman's** The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101).

For example considering the instant specification it is unclear how one skill in the art would treat loss of cardiac muscle contractility associated with heart failure by administering a S16E mutant phospholamban gene to cardiomyocytes in vivo. The RAC advisory panel clearly emphasized the need for a greater understanding of an underlying mechanism that contributes to a disease along with the pathogenesis of the disease. The state of the art at the time of filing was such that the heart failure is almost always a chronic, long-term condition, although it can sometimes develop suddenly. This condition may affect the right side, the left side, or both sides of the heart. The factors that leads to heart failure include family history (congenital heart disease), Ischemic heart disease/Myocardial infarction (coronary artery disease), Heart muscle disease (dilated cardiomyopathy, hypertrophic cardiomyopathy) or inflammation (myocarditis),

Arrhythmia, Hypertension, Cardiac fibrosis, Coarctation of the aorta, Aortic stenosis/regurgitation, Mitral regurgitation, Pulmonary stenosis/Pulmonary hypertension/Pulmonary embolism all leading to pulmonale and Mitral valve disease, arrhythmia or dysrhythmia (See Lip et al, BMJ 320:104-107, 2000). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectation of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. In the instant case, such reasonable detail is lacking. The specification provides no guidance on how to use the compounds of claim 37 as beta-cell growth factors. See Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297 (CA FC 2005) which teaches: "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

In light of the above, the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of delivering the S16E mutated PLB construct into cardiomyocytes in vivo by any and all routes or via intracoronary administration of said construct in vivo resulting in the treatment of loss of cardiac muscle contractility associated with heart failure raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of S16E PLB gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating loss of cardiac muscle contractility associated with hear failure by S16E PLB gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for delivering the S16E construct to cardiomyocytes in vivo, by any and all routes of administration of said construct in vivo, or via intracoronary administration for treatment of loss of cardiac muscle contractility associated with heart failure, the lack of direction or guidance provided by the specification for delivering the S16E construct to cardiomyocytes in vivo, by any and all routes of administration of said construct in vivo, or via intracoronary administration for treatment of loss of cardiac muscle contractility associated with heart failure, the absence of working examples that correlate to delivering the S16E construct to cardiomyocytes in vivo, by any and all routes of administration of said construct in vivo, or via intracoronary administration for treatment of loss of cardiac muscle contractility associated with heart failure, the unpredictable state of the art with respect to delivering the S16E construct to cardiomyocytes in vivo, by any and all routes of administration of said construct in vivo, for treatment of loss of cardiac muscle contractility associated with heart failure, the undeveloped state of the art pertaining to the treatment of loss of cardiac muscle contractility associated with

heart failure, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants have amended the claims to recite that the phospholamban gene encoding protein having an S16E mutation is administered to cardiomyocvtes. Thus, the S16E PLB expression construct is not administered "to any and all myocytes." Rather, the S16E PLB expression construct is administered to cardiomyocytes, where expression of the encoded protein can mediate improved cardiac muscle contractility. Moreover, Applicants respectfully submit that the Examiner's concern that the claims encompass administration "by any and all routes of administration," has been rendered moot by the amendment to claim 18. Specifically, claim 18 has been amended to require that the expression construct be delivered to cardiomyocytes.

These arguments are not persuasive because the claim 18 amendment to cardiomyocytes limits the delivery to cardiomyocytes but not the route of administration of the S16E PLB expression construct which encompasses any route of administration of said construct into cardiomyocytes in vivo. For example, as discussed above, cardiomyocytes, being post-mitotic and terminally differentiated cells, present their own unique challenges and several methods for myocardial gene delivery each presents its own limitations and benefits (**Thompson et al,** Annals of Medicine, 36(Suppl 1): 106-115, 2004) (p 109). For example, direct myocardial injection is burdened with the delivered gene expressing only in and around the small region of myocardium surrounding the needle tack, or pericardial injection is an effective means of transfection in rats and could be proved useful for minimally invasive human delivery if large animal models show similar results (**Thompson et al,** (p 109).

Applicants argue it is respectfully submitted that the skilled artisan would recognize that not any and all routes of administration would be suitable for achieving administration to cardiomyocytes. Indeed, the reference cited by the Examiner (Thompson et al., Annals of Med 36 (Suppl 1): 106-15, 2004) and the primary references therein establish that effective methods of delivery of genes to cardiomyocytes were well-known in the art at the time of filing. For similar reasons, Applicants submit that this rejection does not apply to newly added claim 36, and claims 37-38 depending therefrom, which recites that that the expression construct is administered to cardiomyocytes via intracoronary administration.

These arguments are not persuasive because Applicants have not provided guidance for intracoronary administration of the S16E PLB expression construct in vivo, wherein expression of a therapeutic level of the polynucleotide stimulates cardiac muscle contractility resulting in the treatment of loss of cardiac muscle contractility associated with heart failure as claimed in the newly added claim 36 and its depended claims 37-38. For example, as discussed above, **Beck et al,** reports the technical challenges related to cardiovascular gene transfer are still significant with respect to (i) efficiency of gene delivery, (ii) achievement of high and stable level of transgene expression in a specific cell-type and (iii) design and administration tools and vectors that are safe for clinical application (p 463, bridge 1st to 2nd column). Therefore the prior art challenges the underlying assumption that the S16E mutated PLB transgene will be expressed at sufficient therapeutic levels at the targeted cardiomyocytes, in vivo, for treating loss of cardiac muscle contractility associated with heart failure. With regard to Thompson reference, it teaches intracoronary delivery of βARKct adenovirus down the left circumflex coronary artery into rabbits after myocardial infraction. However, Applicants have failed to correlate the intracoronary administration of the βARKct adenovirus in rabbits after myocardial infraction to the intracoronary delivery of the S16E PLB expression construct in mammalian host suffering

from heart failure resulting in improved cardiac muscle contractility for treating a loss of cardiac muscle contractility as claimed in claim 36 and its depended claims.

Applicants argue the Examiner further asserts that "the transient nature of transgene expression with adenoviral vectors may limit the use of these vectors to the treatment of acute vascular injury and have less utility in treating chronic or progressive disorders such as heart failure and athersclerosis," citing Barbato et al. (Critical Reviews in Clin Lab Sci 40(5):499-545, 2003) (Office Action at page 4). Contrary to the Examiner's assertion, Applicants have demonstrated sustained expression of the S16E PLB transgene in a hamster model of cardiomyopathy (see Applicants' co-pending application Serial No. 09/954,571 (US PG Pub. No. 2002/0032167, filed 9/11/2001). Specifically, Applicants provide at paragraph 0040 of the '571 application that, This effect of AAV-S 16EPLB to mitigate the development of heart failure was further evident at 3-6 months post-gene transfer, with a substantial improvement in % FS ... and mVcf .... The high fidelity left ventricular pressure measurement directly documented that the AAV mediated delivery of the pseudophosphorylation mutant PLB sustained its rescue effect on cardiac contractility for at 3 months post-gene delivery ... displaying an over 50% increase of LV max dP/dt in the S 16EPLB- transferred animals compared to LacZ controls.

These arguments are not persuasive because the instant invention is examined to the extent of the disclosed specification of the instant application under examination. As discussed above the instant specification in the instant case does not provide guidance for intracoronary delivery of the claimed S16E PLB construct resulting in the treatment of a loss of cardiac muscle contractility associated with heart failure. The instant specification merely provides guidance for the amino acid sequence of an H6-PLB (S16E mutant)-ANT protein and an H6-PLB (V49A mutant)-ANT protein (SEQ ID: Nos. 18 and 19 respectively) (specification p 31, lines 23-24).

Therefore, the instant specification has failed to provide guidance for delivering said PLB mutant via intracoronary route in vivo resulting in treating loss of cardiac muscle contractility associated with heart failure for overcoming the limitations of delivering the S16E mutated PLB construct into cardiomyocytes in vivo by any and all routes or via intracoronary administration of said construct in vivo resulting in the treatment of loss of cardiac muscle contractility associated with heart failure raised by the state of the art.

Applicants argue as to the adenoviral vector whose use is discussed by Barbato, et al., it will be appreciated that even transient changes in contractile function in the heart can be beneficial; e.g., in acute therapy pending surgical intervention, such as transplantation (see, e.g., Giordano, et al., Nat. Med., 2:534-539, 1996).

These arguments are not persuasive because Babato et al teach that the transient nature of transgene expression with adenoviral vectors may limit the use of these vectors to the treatment of acute vascular injury and have less utility in treating chronic or progressive disorders such as heart failure and atherosclerosis. Moreover, the incorporation by reference by Giordano with regard to transplantation is not correlatable to the S16E PLB expression construct which encompasses any route of administration of said construct into cardiomyocytes in vivo or via intacoronary delivery resulting in treating loss of cardiac muscle contractility associated with heart failure. Transplantation of the claimed vector has to reach the cardiomyocytes via tissue barrier microenvironment as opposed to intracoronary route where the vector has to reach cardiomyocytes via the vascular system. The delivery of the vector to cardiomyocytes in vivo via transplantation does not provide guidance for overcoming the obstacles of in vivo delivery of the vector via intracoronary route because the vector has to pass through the vascular barriers. Therefore, in view of the lack of guidance in the specification and

in view of the teachings in the art at the time of filing regarding S16E gene therapy for treating loss of cardiac muscle contractility associated with heart failure, the skilled artisan would have to engage in an undue amount of experimentation without a predictable degree of success to implement the present invention as claimed.

Applicants argue that the inventors studied the effects of the S16E PLB transgene in rats with heart failure after myocardial infarction (MI), a model of acquired disease. Specifically, the inventors showed that "in vivo delivery of the S16EPLN gene was highly effective in improving LV function and mitigating adverse remodeling compared with delivery of saline" (see Iwanaga et al., J Clin Investigation 113(5):727-36, 2004 at p. 732, col. 2; copy attached). The results reported provide concrete evidence that treatment of MI rats with S 16E PLB improved contractility in addition to other cardiac function parameters and that such improvement was sustained over the 6-month observation period. The inventors conclude that these finding document that the therapeutic effects of the present methods can be extended to acquired forms of heart failure.

These arguments are not persuasive because at the time of filing the specification fails to provide guidance for a nexus between the function of the S16E gene and its role in mediating improved cardiac muscle contractility. The specification discloses only the amino acid sequence of an H6-PLB (S16E mutant)-ANT protein and an H6-PLB (V49A mutant)-ANT protein (SEQ ID: Nos. 18 and 19 respectively) (specification p 31, lines 23-24). As such an ordinary skilled artisan would have to perform undue experimentation to predict the phenotype of the transgene after its expression in vivo and its function as it is associated with stimulating improved cardiac muscle contractility resulting in treating loss of cardiac muscle contractility associated with loss

of heart failure. It is well known in the art that random integration of a transgene into the host cellular genome is unpredictable with regard to the resulting phenotype in vivo.

Applicants argue in yet another study, S16E PLB gene therapy in sheep with moderate-to-severe pacing- induced heart failure was shown to enhance cardiac contractility in heart failure (see Hoshijima et al., JAmer Coll Cardiology 48(9 Suppl A):A15-A23, 2006 at p. A21, col. 2; copy attached). Taken together these studies establish that the claimed methods are effective in treating heart failure regardless of the particular etiology (e.g., genetic or acquired) of heart failure in each model. In summary, the evidence of record therefore confirms what the Specification asserts: the S 16E phospholamban molecule, delivered to the heart in an expression construct, improves cardiac contractility.

These arguments are not persuasive for the same reasons as discussed above for the Iwanaga et al., J Clin Investigation 113(5):727-36, 2004.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal

disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18, 19, 24, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 70, 71, 72, 98, 99, 100, 101 of copending Application No. 09/954571. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace treatment of heart failure in a patient comprising administering to a patient an expression construct encoding a protein having an S16E mutation. The breadth of the scope of the claims recited in the '571 includes is to treatment of heart failure associated with loss of cardiac muscle contractility in a patient comprising administering to cardiac muscle said S16E PLB mutant nucleic acid and obviously encompasses the S16E PLB mutant nucleic acid as embraced in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants argue that the provisional rejection of claims 18, 19, and 24 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 70-72 and 98-101 of co- pending Application No. 09/954,571 (hereinafter "the '571 application") is respectfully traversed. While not acquiescing to the substantive basis for this rejection, in order to reduce the issues and expedite prosecution, a terminal disclaimer over a patent that may issue from the commonly-owned '571 application is submitted herewith. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The examiner was not able to locate said terminal disclaimer on record. Therefore, the above provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
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